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Dual endothelin antagonism from early diabetic stage is effective in preventing various diabetic complications through both improving organ microcirculation and restoration of altered VEGF signaling

Subrina Jesmin, Nobutake Shimojo, Sayeeda Nusrat Sultana, Majedul Islam, Sohel Zaedi, Satoru Kawano, Taro Mizutani, Takashi Miyauchi

Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan
E-mail address: jsubrina@gmail.com (S. Jesmin)

Purpose: Diabetes mellitus causes both macrovascular and microvascular complications. Several treatments effectively prevent macrovascular complications such as stroke and AMI. Because current treatments are insufficient to prevent diabetic microvascular complications such as diabetic retinopathy and nephropathy, erectile dysfunction and cardiomyopathy, we aimed to study a possibility of endothelin antagonism on these microvascular complications. Vascular endothelial growth factor (VEGF) was reported to cause a central trigger leading to the structural and functional changes in diabetic complications, and we also assessed restoration of VEGF signaling by endothelin antagonism. Since both ET-A and ET-B receptors in vascular smooth muscles are involved in the microvascular contraction/proliferation, we applied the ET-A/B dual antagonist SB209670 to rats. Methods: Male Sprague–Dawley rats were administered citrate saline (vehicle) or streptozotocxin (65 mg/kg IP). One week after injection, rats were separated into those receiving SB209670 or vehicle by osmotic mini pump for 2 weeks. Results: We found reduction of VEGF signaling with capillary density in diabetic heart and penile tissues, whereas found overexpression of VEGF signaling in diabetic retina and kidney. SB209670 administration was effective in preventing development and progression of various diabetic complications through modification of respective microcirculation and restoration of VEGF signaling; SB209670 prevents diabetic cardiomyopathy through restoration of VEGF reduction, prevents erectile dysfunction through restoration of VEGF reduction, and prevents the development of diabetic retinopathy and nephropathy through restoration of VEGF overexpression. Conclusion: Dual endothelin antagonism by SB209670 is effective in preventing various diabetic microvascular complications such diabetic retinopathy and nephropathy, erectile dysfunction and cardiomyopathy through both improving organ microcirculation and the restoration of altered VEGF signaling.

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Lifestyle modification induces decreased central blood pressure and increased serum testosterone concentration in overweight and obese men

Hiroshi Kumagai[a], Asako Miyaki[b], Rina So[b], Takehiko Tsujimoto[b], Takashi Miyauchi[c], Kiyoji Tanaka[b], Seiji Maeda[b]

[a]*Graduate School of Comprehensive Human Sciences, University of Tsukuba, Japan*
[b]*Faculty of Health and Sport Sciences, University of Tsukuba, Japan*
[c]*Faculty of Medicine, University of Tsukuba, Japan*
E-mail address: kumazin7@gmail.com (H. Kumagai)

Background: Increase in central blood pressure (cBP) is a risk factor for cardiovascular disease. cBP is higher in the obese individuals than the age-matched normal-weight humans. We previously demonstrated that lifestyle modification decreases cBP in obese men. However, the mechanism underlying lifestyle modification-induced decrease in cBP has not been elucidated. Testosterone is a kind of androgens and known to have cardioprotective effect. The aim of the present study was to examine whether testosterone is involved in the mechanism underlying the decrease in cBP with lifestyle modification. Methods: Thirteen overweight and obese men (age: 50 ± 2 yrs, BMI: 30 ± 1 kg/m^2) completed a 12-week lifestyle modification program (well-balanced 1680 kcal/day diet and brisk walking for 40–60 min/day, 3 days/week). Before and after the program, we measured cBP and serum testosterone level in all participants. Results: After the program, a significant weight loss was observed (−12.7 ± 1.3 kg, $P < 0.05$). cBP significantly decreased and serum testosterone level significantly increased after the program (both $P < 0.05$). Moreover, there was a significant relationship between the change in cBP and that in serum testosterone level ($r = -0.63$, $P < 0.05$). Conclusions: After the 12-week lifestyle modification, cBP decreased and serum testosterone level increased in the overweight and obese men. We also demonstrated that there was a negative relationship between the change in cBP and that in serum testosterone level. These findings suggest that increased serum testosterone level may partly contribute to the decrease in central blood pressure in overweight and obese men.

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Characterization of the binding of [125I]GLP-1(9-36) amide, the Major metabolite of the insulin secretagogue, glucagon-like peptide 1 (GLP-1) and function of the unlabelled peptide in murine aorta

Rhoda E. Kuc[a], Janet J. Maguire[a], Keith Siew[a], Sheena Patel[b], Margaret Jackson[b], Anthony P. Davenport[a]

[a]*Clinical Pharmacology Unit, Cambridge, MA, USA*
[b]*Pfizer, Cardiovascular Medicine, Cambridge, MA, USA*
E-mail address: apd10@medschl.cam.ac.uk (R.E. Kuc)

Glucagon-like peptide 1 (GLP-1) is an insulin secretagogue synthesized in the intestine and released in response to meal ingestion and efficiently lowers blood glucose in type 2 diabetic patients. GLP-1(7-36) has a very short half-life and is rapidly metabolized by dipeptidyl peptidase IV to the major metabolite GLP-1(9-36)-amide, often thought to be inactive. Inhibitors of this enzyme are widely used to treat diabetes. However, it is unclear whether GLP-1(9-36) mediates functional activity via specific receptors. Following pre-incubation of fresh frozen section of cryostat sections (Bregma ~−2.5) from adult mouse brains, binding assays were carried out using increasing concentration of either [125I]GLP-1(7-36) or [125I]GLP-1(9-36) for 90 min at room temperature. Non-specific binding was defined by 10 μM of the GLP-1(7-36) and GLP-1(9-36). In functional experiments, mouse aortae were mounted in wire myographs and the effect of increasing concentrations of each peptide was measured.

Ligand binding (mouse brain, n = 4)	KD (nM)	BMAX (fmol/mg)	nH
[125I]GLP-1(7-36)	1.29 ± 0.26	57.0 ± 14.5	0.96 ± 0.06
[125I]GLP-1(9-36)	0.214 ± 0.08	2.69 ± 0.74	1.06 ± 0.05
Vasoconstrictor Assay (mouse aorta, n = 3)	**pD2 (nM)**	**EMAX % KCl maximum**	
GLP-1(7-36)	7.69 ± 0.24	35 ± 8%	–
GLP-1(9-36)	7.57 ± 0.64	25 ± 7%	–

In the mouse brain both labeled peptides bound with a single high sub-nanomolar affinity, with Hill slopes close to unity. The density of receptors was an order of magnitude lower for [125I]GLP-1(9-36). In functional experiments both peptides had similar potencies. These results suggest that GLP-1(9-36) has functional activity at the GLP1 receptor.

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